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SERVICE INVENTION

Process for Preparing Spiro-oxindole Derivatives and of Drug Preparations Containing Same

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The present invention pertains to new racemic and optically active 3-spiro-oxindole derivatives according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom,

Z and W denote, independently from one another, a nitrogen atom or a =CH- or =CR- group, in which R denotes an alkyl group containing 1-4 carbon atoms, providing that Z and W cannot simultaneously denote a nitrogen atom,

and therapeutically suitable acid addition salts thereof, as well as to a process for preparing same by reacting an isatinylidene derivative according to the general formula (II), in which X, W, Z, and R have the meanings given above, with trimethylsulfoxonium methylide prepared in situ, in an organic solvent, under an inert gas atmosphere, and by optionally resolving the compounds according to general formula (I) obtained and/or converting them into therapeutically suitable acid addition salts after separating the C_3 isomers.

The compounds according to the general formula (I) are novel and possess therapeutic action, namely, mainly antihypoxic and anticonvulsive actions and inhibitory action on established brain edema, so that the drug preparations containing the compounds according to the general formula (I) as active ingredients as well as the process for preparing same are also within the scope of the present invention.

In the general formulas, the halogen atoms denoted by X may be a fluorine, chlorine, bromine or iodine atom. The alkyl group containing 1-4 carbon groups denoted by R may be a straight-chain or branched alkyl group, such as a methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec.*-butyl group, and preferably a methyl group.

Some of the compounds according to the general formula (II) used as starting compounds in the process according to the present invention are novel. The compound containing the substituents X = H, W = N, Z = CH and R = H has been known; it was synthesized by reacting isatin and 2-picoline [Akkerman et al., *Receuil*, *73*, 629 (1954)]. The compounds according to the general formula (II) which contain the other substituents may be obtained by dehydrating a compound according to the general formula (III) (Example 4). Some of the compounds according to the general formula (III) are also novel; one of their representatives, the compound containing the

substituents X = H, W = N, Z = CH, and R = H, is described in the above-mentioned article. The compounds according to the general formula (III) may be prepared according to Example 5 by reacting isatin or a corresponding, halogenated isatin and 2- or 4-picoline or 2-picoline containing the desired substituent at the position of R.

The preparation of trimethylsulfoxonium methylide from trimethylsulfoxonium halide, preferably the iodide, has been known [E. J. Corey et al., *J. Am. Chem. Soc.*, *87*, 1353 (1965)].

The compounds according to the present invention are novel, and we confirmed their pharmacological actions by the following investigations.

Antihypoxic Action

We used male rats with a body weight of 200 g with spontaneous hypertension (SH) and male CFLP mice with a body weight of 24-26 g for the investigations, with 10 animals in each group. All compounds tested were administered suspended in Tween-80 p.o. in a volume of 10 m*L*/kg of body weight 1 hour before the experiment.

Anoxic Asphyxia (AA) in Mice

The animals were treated with the compounds to be tested after fasting for 16 hours. One hour after the treatment, the animals were placed into hermetically sealed 100-m*L* glass jars. The time elapsing between the closure and the last respiratory movement was recorded. The animals that survived 30% longer than the average survival time of the groups treated with the vehicle were considered to be protected.

Hypobaric Hypoxia (HH) in Mice

After fasting for 16 hours and the 1-hour pretreatment, the animals were placed into a 6-*L* desiccator and the pressure was reduced to 170 Hg mm within 20 sec after closing the desiccator. The survival time was recorded from this point in time onward until the last respiratory movement

of the animals. The animals that survived 100% longer than the average survival time of the control group under the effect of the treatment were considered to be protected.

Hypobaric Hypoxia in SH Rats (SHR HH)

The experimental setup was the same as described in the above investigation. The animals that survived 30% longer than the average survival time of the control group were considered to be protected.

Anticonvulsive Action

Male CFLP mice with a body weight of 18-22 g, 10 animals in each group, were used to investigate the anticonvulsive action. All compounds tested were administered suspended in Tween-80 p.o. in a volume of 10 m*L* per kg of body weight 1 hour before the experiment.

Maximum Electric Shock in Mice (MES)

An attack of spasm was induced after the 1-hour pretreatment by means of electric shock elicited via a corneal electrode (20 mA, 0.2 sec). The animals in which the tonic spasm of the extensor muscle failed to develop were considered to be protected.

Metrazole Spasm in Mice (MET)

The animals were administered 125 mg/kg of Metrazole (pentylenetetrazole) s.c. 1 hour after the pretreatment with the compounds to be tested. The failure of the tonic spasm of the extensor muscle to develop and survival were considered to represent protection.

The ED_{50} values of the compounds and the confidence intervals were calculated from the % of the protected animals in the above tests by probit analysis.

The results obtained in the antihypoxic and anticonvulsive tests are shown in Table 1.

Table 1

ED_{50} values of the compounds tested and of the reference compounds (mg/kg)

Compound	Example	AA	HH	SHR HH	MES	MET
1407579	2	35.8	30.6	7.4	43.6	33.0
Vincamine		50.0	60.7	27.9	38.9	50.0
Nimodipine		85.3	>100	8.0	>60.0	47.0
Hydergine		NE	NE	50.0*	NE	NE

NE: Ineffective even at an oral dose of 100 mg/kg.

*: Maximum effect; 40% survival at a dose of 50 mg/kg.

Effect on Brain Edema

The effects of the compounds on brain edema were investigated according to the method described below (P. Linnée, M. Quiniou, C. Godin and J. B. Le Polles: Brain Edema Induced by Triethyltin in Rats. Its Value and Limitations as a Method for the Study of Agents Against Brain Edema. *Ann. Pharmaceutiques françaises*, *42*, 1984, pp. 431-442).

Male Hannover-Wistar rats were used for the investigations. Brain edema was induced by treatment with triethylene chloride (TET) at a dose of 2.5 mg/kg for 5 days. The first dose of the compounds was administered 1 hour after the TET treatment, and the treatment was then repeated after 6 hours. All treatments were oral. Each group consisted of 7 animals; the control group was treated with the solvent of TET and the vehicle of the compound to be tested, and the TET group was also treated with the vehicle of the compounds to be tested in the above-described manner and at the times indicated above.

The animals were decapitated on day 5 of the treatment, 2 hours after the treatment with the test compound. The whole brain was rapidly removed, rinsed with cold physiological saline solution, the moisture was removed on filter paper, and the fresh weights of the brains were determined on an electric balance to an accuracy of one tenth of one mg, and the brains were placed on aluminum foils weighed in advance. The brains were then dried at 90°C for 92 hours, after which the gross dry weight of the brains (dry weight of the brain plus the weight of the aluminum foil) was again determined by weighing.

With the knowledge of the dry and fresh weights, we calculated the water content in the brain and the effect of the treatment with the compounds, which we expressed as the percentage of protection from the following formula:

$$\text{Protection, \%} = \frac{(\text{TET-Ko}) - (\text{TET-V})}{(\text{TET-Ko}) - (\text{Veh-Ko})} \times 100$$

in which (TET-Ko) = average water content in the brains of the animals treated with TET and the vehicle (in %),

(TET-V) = average water content in the brains of the animals treated with TET and the compound (in %), and

(TET-Ko) = average water content in the brains of the animals treated with distilled water and the vehicle (in %). [sic - should be Veh-Ko - Tr.Ed.].

The deviations in the changes occurring in the brain water contents (and in the dry weight) under the effect of the treatments were compared according to Student's t-test. If the brain water content showed a significant difference from the group treated with TET under the effect of the treatment, the change was also considered to be significant.

The results of the measurements are shown in Table 2.

Table 2

Effects of the compound tested (1407579, Example 2) and of the reference compounds on TET-induced brain edema in rats

Treatment	Dose (µmoles/kg)	Brain water content (% ± SEM)	Protection (%)
Distilled water + vehicle		77.91	-
TET + vehicle		80.22[a]	
TET + 1407579	100	77.98[***]	97.1[***]
TET + vincamine	100	79.50[***]	69.1[***]
Distilled water + vehicle	-	77.76	-
TET + vehicle	-	80.73[a]	-
TET + Hydergine	30[1]	79.97	25.6
TET + vincamine	100	78.89[***]	62.0
Distilled water + vehicle	-	78.48	-
TET + vehicle	-	80.35[a]	-
TET + nimodipine	100	80.73	-20.2

[a] Significant difference from the group treated with distilled water; $p < 0.001$

[***] Significant difference from the group treated with TET + vehicle; $p < 0.001$

[1] The dose of Hydergine was 30 mg/kg in the above experiment.

Interpretation of the Results Obtained:

In the case of the measurement of the antihypoxic and anticonvulsive actions, the data in Table 1 indicate that one of the compounds found to be most effective among the compounds according to the present invention, namely, the compound 1407579 according to Example 2, has a pronounced antihypoxic action: Its ED_{50} values considerably exceed the ED_{50} values obtained with all reference compounds for both asphyxia-induced anoxia and hypobaric hypoxia. It is remarkable that the compound was most effective in the hypoxia test carried out on rats with spontaneous hypertension (SHR HH); its effect seems to be even better in these animals than that of nimodipine, which was found to be most active. All this shows that the compound considerably enhances the hypoxia tolerance of the brain.

The anticonvulsive action of compound 1407579 is not negligible, either; it was about 1.5 to 2 times more effective in the spasm test performed than vincamine and nimodipine (Hydergine was practically ineffective in these tests). It has been known that the oxygen supply of the brain is normal during spastic activity, but the oxygen demand of the nerve cells increases as a consequence of the increased metabolic activity, and their oxygen uptake capacity also decreases, i.e., a relative hypoxia develops. As a consequence, the lasting excitation spreads over an increasing number of nerve cells: The spasm becomes generalized. It can be assumed that the anticonvulsive action of compound 1407579 is linked with its facilitating the oxygen uptake by the nerve cell and/or by preventing the relative hypoxia from causing cellular - and consequently functional - damage.

In the case of the measurement of the effect on brain edema: The data presented in Table 2, which were obtained in experiments carried out at different times, indicate that the method is very well reproducible, because

(1) the brain water content in the control animals,

(2) the increase that can be elicited in the water content with TET, and

(3) the protective action of vincamine, which was used as a reference compound in as many as two experiments,

were constant from one experiment to the next, within the limits of the biological spread.

To ensure comparability, the doses of the compounds tested were molarly equal. In view of the fact that Hydergine (dihydroergotoxine mesylate) is a mixture of four compounds at a defined ratio and no exact molecular weight can be stated as a result, this compound was used at a dose expressed in mg/kg. Another factor to consider was that if a molar dose corresponding to the "average" molecular weight of Hydergine were used, this dose would be considerably outside the pharmacological doses.

The data in the table show clearly that the effect of compound 1407579, which was found to be most effective among the compounds according to the present invention, at an equal molar dose (31.5 mg/kg) considerably surpasses the edema-inhibiting actions of all reference compounds tested, including vincamine (35 mg/kg), Hydergine (30 mg/kg) and nimodipine (41.7 mg/kg).

It is particularly remarkable that the compound is more effective than even vincamine, whose TET edema-inhibiting action has been well known (see references cited in the methods section).

Nimodipine, which has been known to be a Ca channel blocker and which also has antihypoxic actions, exerted just the opposite effect, according to the data in Table 1, i.e., it even seemed to exacerbate the brain edema induced by TET. In agreement with the data published by other authors (J.-C. Lamar, M. Beaughard, C. Bromont and Poignet: Effects of Vinpocetine in Four Pharmacological Models of Brain Ischemia, in: *Pharmacology of Brain Ischemia*, ed.: J. Krieglstein, Elsevier Science Publishers B.V. Amsterdam, 1986, pp. 334-339), Hydergine failed to display a significant protective action under these experimental conditions.

The long-term administration of triethyltin induces severe edema in the central nervous system, i.e., a considerable increase in the water content in the brain. Even though both the white matter (myelin) and the gray matter are affected, the increase in the water content is more pronounced in the white matter. TET also leads to considerable damage to the metabolic activity of the brain: It inhibits the cellular respiration and oxidative phosphorylation and the burning up of glutamate, glucose and succinate (and of pyruvate at a higher concentration). The Na content in the

brain tissue increases considerably (at unchanged K content), and the catecholamine and serotonin reserves are partially depleted (see: D. E. McMillan and G. R. Wenger: Neurobehavioural Toxicology of Trialkyltins. *Pharmacological Review*, *37*, 1985, pp. 365-379). The damage to the brain cells leads to functional damage to the brain: The learning and memory performance of the animals exposed to TET is considerably impaired.

Many of the above-described cellular changes (damage) can also be observed in ischemia and hypoxia (see B. K. Siesjö, Cell Damage in the Brain: A Speculative Synthesis. *J. Cerebral Blood Flow and Metabolism*, 1, 1981, pp. 155-185), and they contribute to the development of the cellular damage (cell death) and of the functional damage (cognitive functions: memory and learning).

Based on the summary and the evaluation of the results of the investigation, it can be seen that compound 1407579, Example 2, which was found to be the most effective of the compounds according to the present invention, has a considerable antihypoxic, anticonvulsive action and an inhibiting action on TET-induced edema. Its acute toxicity is low: Its LD_{50} is >1,000 mg/kg. Based on all this, both the compound 1407579 and the compounds according to the general formula (I) can be expected to be suitable for the prevention and the treatment of primary damage (e.g., edema) caused by hypoxia and ischemia of various etiologies and of their sequels (e.g., cognitive damage such as dementia).

The present invention will be described in detail below.

In the process according to the present invention, the isatinylidene derivative according to the general formula (II) is reacted with trimethylsulfoxonium methylide, which is prepared in situ from trimethylsulfoxonium iodide with a base, preferably with sodium hydride.

The reaction is carried out by adding the solid trimethylsulfoxonium iodide to the solution of oil-free sodium hydride in a dipolar aprotic solvent, e.g., dimethylsulfoxide, dimethylformamide, dimethylacetamide, and advantageously dimethylformamide, under an inert gas atmosphere, e.g., under a nitrogen or argon atmosphere, preferably under an argon atmosphere, while cooling with

ice. The corresponding compound according to the general formula (II) is added to the carbanion solution in dimethylformamide thus obtained. The reaction takes place in 2-3 hours at a temperature between 0°C and 25°C; the course of the reaction is monitored by TLC.

A mixture of the C_3 isomers of the compounds according to the general formula (I) is formed in the process according to the present invention. In one of the isomers, the oxo group and the hydrogen atom bound to the C_3 atom are located on the same side of the plane defined by the cyclopropane ring (compound 3β); the oxo group and the C_3 hydrogen atom are located on opposite sides of the plane (compound 3α) in the case of the other isomer.

The reaction is diastereoselective; the two isomers are formed in greatly different proportions. The ratio of the 3α and 3β products is approximately 9:1 in favor of compound 3β.

The Seebach convention (Seebach et al., *Angew. Chem. Int. Ed. Engl.*, 21 (1982), pp. 654-660) is used to designate the stereochemistry in the names of the examples.

After the reaction has taken place, the compound according to the general formula (I) may be advantageously isolated by breaking the reaction mixture by carefully adding water while cooling with ice and subsequently removing the solvent by evaporation to dryness. The residue is divided between a solvent immiscible with water, such as ethyl acetate, dichloromethane, chloroform, etc., and water, preferably between ethyl acetate and water, washed with water, and the organic phase is then concentrated by evaporation after drying. The residue, which contains the above-described mixture, is processed by means of a suitably selected solvent, such as ethyl acetate, acetone, methanol, ethanol, isopropyl alcohol or a suitable mixture thereof by separating it into the C_3 isomers by fractionated crystallization. The desired principal product 3β is isolated according to a suitable method, e.g., by filtration. The mother liquid obtained by crystallization is used to isolate the minor product. The minor product is isolated by column chromatography. The column chromatographic isolation is performed on a silica gel column in a halogenated solvent containing 10% of an alcohol with a short carbon chain, e.g., in chloroform-methanol, chloroform-ethanol, dichloromethane-methanol, dichloromethane-ethanol mixture, and most advantageously in chloroform containing 10% of methanol. The product 3β left in the mother liquor is obtained at Rf

= 0.6, and the minor isomer 3α is obtained at Rf = 0.5. After chromatography, the compounds are isolated by triturating the syrupy substance left after the removal of the organic solvent by evaporation in a suitably selected organic solvent, such as ether, ethyl acetate, acetone, preferably ethyl acetate and isolating the crystals precipitated in a suitable manner, e.g., by filtration.

The racemic compound according to the general formula (I) obtained is optionally resolved and/or converted into acid addition salts. The resolution of the compounds according to the general formula (I) may be performed according to any known resolving process. An optically active acid or compound of an acidic nature which is usually used, e.g., tartaric acid, dibenzoyltartaric acid, camphorsulfonic acid, di-*p*-toluenetartaric acid, dibenzoyltartaric acid mono-dimethylamide, etc., may be used as the resolving agent. An optically active natural amino acid may be used as well.

The resolution is performed in a suitably selected inert organic solvent, e.g., a protic organic solvent, such as an alkanol containing 1-4 carbon atoms, such as methanol or ethanol, or in a chlorinated hydrocarbon, preferably an aliphatic chlorinated hydrocarbon, such as dichloromethane or dichloroethane, or in a mixture thereof. It is also possible to use a dipolar aprotic solvent, e.g., a ketone, preferably acetone. The resolution is performed under atmospheric pressure between 0°C and the boiling point of the solvent used, preferably at a temperature between 20°C and 50°C. The diastereomeric acid addition salts formed with the optically active acid are separated by crystallization, after which the desired base may be optionally released from the acid addition salt obtained. The base release is preferably performed by dissolving or suspending the salt in water or in water and an organic solvent immiscible with water, such as halogenated aliphatic or aromatic hydrocarbons, open-chain or cyclic ethers, e.g., dichloromethane, chloroform, ether, toluene, etc., and by subsequent alkalization with an inorganic base, such as alkaline earth carbonates, such as potassium or sodium carbonate, or ammonia, and by subsequently extracting the base, if desired, with one of the above-mentioned solvents immiscible with water. If desired, the racemic or optically active compounds according to the general formula (I) may be converted into therapeutically suitable acid addition salts.

The salt formation is carried out in an inert organic solvent, e.g., an alcohol containing 1-3 carbon atoms or acetone, or in halogenated hydrocarbons, e.g., chloroform, or in a mixture thereof

by dissolving the compound according to the general formula (I) in one of the above solvents and subsequently adding the corresponding acid to the solution until the pH value of the mixture becomes slightly acidic (pH approximately 5-6). The salt formation may also be carried out by adding to the solution the solution of the calculated amount of the desired acid in one of the above solvents. The acid addition salt precipitated is then isolated from the reaction mixture in a suitable manner, e.g., by filtration.

The active ingredient according to the general formula (I) is converted into therapeutic preparations with nontoxic, inert solid or liquid vehicles and/or inactive ingredients suitable for parenteral or enteral administration, which are usually used in therapy. The suitable vehicles include, e.g., water, gelatin, lactose, milk sugar, starch, pectin, magnesium stearate, stearic acid, talc, vegetable oils, such as peanut oil, olive oil, etc. The active ingredient may be prepared in the form of the usual therapeutic preparations, e.g., especially in the solid form, e.g., in the form of rounded or angular tablets, coated tablets, capsules, pills, suppositories, etc. The amount of the solid vehicle may vary within a broad range, preferably between about 25 mg and 1 g. The preparations may optionally also contain usual therapeutic inactive ingredients, e.g., preservatives, stabilizers, wetting agents, emulsifying agents, etc. The preparations may be prepared according to the usual methods, e.g., by screening the components, mixing and granulation and tabletting in the case of solid preparations. The preparations may also be subjected to additional operations employed in pharmaceutical technology, e.g., sterilization.

The process according to the present invention will be illustrated by the following examples, without our claims being limited to these examples.

Example 1

Separation of (±)-1,3-1-(2-Pyridyl)-spiro[cyclopropane-1,3'[3H]-indol]-2'(1'H)-one (1407057, 3β) and (±)-1,3-u-(2-pyridyl)-spiro[cyclopropane-1,3'[3H)-indol]-2'(1'H)-one (3α)

a) 2.0 g of sodium hydride dispersion are made oil-free under an argon atmosphere by washing with *n*-hexane (2 x 10 m*L*), after which they are dissolved in 80 m*L* of anhydrous

dimethylformamide, cooling with an ice water bath. 6.8 g (30 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution within about 5 minutes, after which the mixture is stirred for another 15 minutes. 4.44 g (20 mmoles) of α-isatinylidene-2-methylpyridine are added in small portions to the above solution, after which the solution is stirred for 2 hours while the ice bath melts. Twenty m*L* of water are added to the reaction mixture and the mixture is concentrated by evaporation under motor vacuum. The evaporation residue is dissolved in a mixture of 100 m*L* of ethyl acetate and 50 m*L* of water. The phases are separated, the organic phase is washed with 2 x 50 m*L* of water, after which it is dried over anhydrous sodium sulfate. The filtered solution is concentrated by evaporation under vacuum. The 4.5 g of oily crude product thus obtained is a mixture of the 3β and 3α isomers at a ratio of 9:1.

The 3β isomer is first separated by fractionated crystallization: The crude product is dissolved in 15 m*L* of hot acetone, after which it is clarified with animal charcoal. The filtered solution is allowed to stand overnight in a refrigerator. The desired crystalline substance is filtered out, washed with cold acetone (5 m*L*), and dried. 2.02 g of the 3β isomer are thus obtained.

The mother liquor obtained on crystallization is subjected to silica gel column chromatography, using a mixture of chloroform and methanol at a ratio of 9:1 as the eluent. The compound eluted at Rf = 0.6 is the residue of the 3β isomer; this is concentrated by evaporation and crystallized, thus obtaining an additional 0.7 g of the compound 3β.

Total yield: 58%

Melting point: 170-172°C

IR (KBr): 3450, 1710, 1620, 1590 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 2.22 (dd, 1H, *J* = 9+4 Hz, H2β), 2.66 (dd, 1H, *J* = 8+4 Hz, H2α), 3.34 (dd, 1H, *J* = 9+8 Hz, H3), 6.65 (dd, 1H, *J* = 7.5+1.5 Hz, H4'), 6.73 (td, 1H, *J* = 7.5 7.5+1 Hz, H5'), 6.90 (dd, 1H, *J* = 7.5+1 Hz, H7'), 7.07 (td, 1H, *J* = 7.5+7.5+1 Hz, H6'), 7.17 (m, 1H, *J* = 7.5+5+1.5 Hz, H5''), 7.23 (m, 1H, *J* = 7.5+1.5+1 Hz, H3''), 7.57 (td, 1H, *J* = 7.5+7.5+2 Hz, H4''), 8.63 (m, 1H, *J* = 5+2+1 Hz, H6''), 8.81 (bs, 1H, H1').

b) The compound eluted at Rf = 0.5 during the column chromatography is the 3α isomer.

Thirty mg of substance are obtained after evaporation and crystallization.

Yield: 0.6%

Melting point: 199-201°C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 2.09 (dd, 1H, *J* = 9+5 Hz, H2α), 2.49 (dd, 1H, *J* = 8.5+5 Hz, H2β), 3.29 (dd, 1H, *J* = 9+8.5 Hz, H3), 6.81 (dt, 1H, *J* = 7.5+1+1 Hz, H7'), 6.93 (m, 1H, *J* = 7.5+1.5+1 Hz, H4'), 6.99 (td, 1H, *J* = 7.5+7.5+1 Hz, H5'), 7.14 (m, 2H, H6'+H5''), 7.38 (m, 1H, *J* = 7.5+1.5+1 Hz, H3''), 7.63 (td, 1H, *J* = 8+7.5+2 Hz, H4''), 8.50 (dd, 1H, *J* = 5+2+1 Hz, H6''), 9.30 (bs, 1H, H1').

Example 2

(±)-1,3-1-(2-Pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-[3H]-indol]-2'(1'H)-one (1407579, 3β)

2.0 g of a sodium hydride dispersion are made oil-free by washing with *n*-hexane under an argon atmosphere, and then dissolved in 60 m*L* of anhydrous dimethylformamide and cooled with an ice water bath. 6.8 g (30 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution, after which the mixture is stirred for 15 minutes. Then, 6.02 g (20 mmoles) of α-(5-bromo)-isatinylidene 2-methylpyridine (see Example 4) are added to the solution, and the mixture is stirred at room temperature for 2 hours.

Then, 15 m*L* of water are added to the reaction mixture, after which it is evaporated to dryness under motor vacuum. The residue is dissolved in a mixture of 300 m*L* of ethyl acetate and 100 m*L* of water, and the phases are separated. The organic phase is washed with 2 x 50 m*L* of water and dried over anhydrous sodium sulfate. The filtered solution is concentrated to about 20 m*L* by evaporation under vacuum. The crystalline substance precipitated is filtered and washed with 5 m*L* of cold ethyl acetate.

2.2 g of the title compound are thus obtained. Another 0.94 g of product are additionally obtained in the course of the column chromatography of the mother liquor according to Example 1.

Yield: 49.9%

Melting point: 199-203°C.

Elemental analysis based on the empirical formula $C_{15[?]}H_{11[?]}N_2OBr$ (molecular weight: 315.15):

Calculated: C = 57.16%, N = 3.51%, N = 8.88%, Br = 25.35%.

Found: C = 57.09%, N = 3.60%, N = 8.73%, Br = 25.25%.

IR (KBr): 3400, 1680, 1650, 1600, 1570, 1450, 1410, 1300 cm^{-1}.

^{1}H-NMR ($CDCl_3$ + DMSO, 400 MHz) δ ppm: 2.27 (dd, 1H, *J* = 9+4.5 Hz, H2β), 2.63 (dd, 1H, *J* = 8+4.5 Hz, H2α), 3.36 (dd, 1H, *J* = 9+8 Hz, H3), 6.78 (d, 1H, *J* = 8 Hz, H7'), 6.79 (d, 1H, *J* = 2 Hz, H4'), 7.19 (dd, *J* = 8+2 Hz, H6'), 7.29 (m, 2H, H3"+H5"), 7.70 (td, 1H, *J* = 7.5+5+2 Hz, H4"), 8.70 (m, 1H, *J* = 5+2+1 Hz, H6"), 9.65 (bs, 1H, H1').

Example 3

(±)-1,3-u-(2-Pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-[3H]-indol]-2'-(1'H)-one (1408458, 3α)

The procedure described in Example 2 is followed in every respect, and the title compound is then obtained in the course of column chromatography of the mother liquor obtained on crystallization according to Example 1.

Yield: 0.31 g, 5.0%

Melting point: 231-232°C

IR (KBr): 3375, 1705, 1685, 1620, 1580 cm^{-1}.

^{1}H-NMR ($CDCl_3$ + DMSO, 400 MHz) δ ppm: 6.81 (d, 1H, *J* = 9+5 Hz, H2α), 3.28 (dd, 1H, *J* = 9+8 Hz, H3), 6.81 (d, 1H, *J* = 8 Hz, H7'), 7.07 (d, 1H, *J* = 2 Hz, H4'), 7.16 (m, 1H, *J* = 7.5+5+1.2 Hz, H5"), 7.27 (dd, 1H, *J* = 8.2 Hz, H6'), 7.37 (m, 1H, *J* = 7.5+1.2 Hz, H3"), 8.50 (m, 1H, *J* = 5+2+1 Hz, H6"), 9.79 (bs, 1H, H1').

Example 4

(Z)-α-(5-Bromo)-isatinylidene-2-methylpyridine (III-→II) (1407555)

Thirty-eight g (0.2 mole) of *p*-toluenesulfonic acid monohydrate and 15.9 g (50 mmoles) of α-[2-oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2-methylpyridine (see Example 5) are refluxed in 1,000 m*L* of toluene for 24 hours, using a water separator attachment, after which the mixture is evaporated to dryness. The evaporation residue is dissolved in a mixture of 300 m*L* of water and 50 m*L* of methanol, and a sodium hydroxide solution (8 g of NaOH per 160 m*L* of water) is added dropwise to the solution while stirring intensely. The yellow crystalline substance formed is filtered off, washed with 3 x 100 m*L* of water, and then rinsed with 30 m*L* of methanol. 14.56 g of the title compound are thus obtained.

Yield: 97%

Melting point: 250-253°C.

Elemental analysis based on the empirical formula $C_{14}H_9N_2OBr$ (molecular weight: 301.14):

Calculated: C 55.83%, H = 3.01%, N = 9.30%, Br = 26.53%.

Found: C 55.79%, H = 3.07%, N = 9.19%, Br = 26.47%.

IR (KBr): 3420, 3180, 1720, 1700, 1610, 1580 cm^{-1}.

^{1}H-NMR δ($CDCl_3$ + DMSO-d_6, 400 MHz): 6.78 (dd, 1H, *J* = 8.1+1 Hz, H-7), 7.32 (dd, 1H, *J* = 8.1+2 Hz, H-6), 7.33 (m, 1H, *J* = 8+5+1 Hz, H-5'), 7.65 (dd, 1H, *J* = 2+1 Hz, H-4), 7.66 (s, 1H, -CH), 7.83 (m, 1H, *J* = 8.1+8+1.8 Hz, H-4'), 8.71 (m, 1H, *J* = 5+1.8+0.9 Hz, H-6'), 8.10 (m, 1H, *J* = 8.1+1+0.9 Hz, H-3'), 10.12 (bs, 1H, NH).

Example 5

α-[2-Oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2-methylpyridine (III) (1407554)

48.8 g of 5-bromo-isatin monohydrate (0.2 mole) are suspended in 100 m*L* of picoline, and then refluxed for 3 hours. Fifty m*L* of ethanol are added to the hot solution, and the mixture is allowed to cool to room temperature. The crystals precipitated are filtered and washed with 2 x 20 m*L* of ethanol. 50.9 g of the title compound are thus obtained.

Yield: 79.8%

Melting point: 218-221°C.

Elemental analysis based on the empirical formula $C_{14}H_{11}N_2O_2Br$ (molecular weight: 319.16):

Calculated: C = 52.68%, H = 3.47%, N = 8.77%, Br = 25.0%.

Found: C = 52.70%, H = 3.44%, N = 8.81%, Br = 25.09%.

IR (KBr): 3320, 1690, 1600, 1530, 1460 cm^{-1}.

^{1}H-NMR δ ($CDCl_3$ + DMSO-d_6, 100 MHz):

3.20 + 3.34 (both d, 1+1H, *J* = 13 Hz, -CH_2), 5.1 (bs, 1H, OH), 6.68 (dd, 1H, *J* = 8.5+1 Hz, H-7), 6.97 (dd, 1H, *J* = 2+1 Hz, H-5), 7.21 (m, 1H, *J* = 8+5+1 Hz, H-5'), 7.28 (dd, 1H, *J* = 8.5+2 Hz, H-6), 7.30 (m, 1H, *J* = 8+1+1 Hz, H-3'), 7.65 (m, 1H, *J* = 8+8+1.6 Hz, H-4'), 8.44 (m, 1H, *J* = 5+1.6+1 Hz, H-6'), 10.06 (bs, 1H, NH).

Example 6

(±)-1,3-1-(6-Methyl)-2-pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-[3H]-indol]-2'(1'H)-one (1408278, 3β)

2.5 g of sodium hydride dispersion are made oil-free by washing with *n*-hexane under an argon atmosphere, then dissolved in 75 m*L* of anhydrous dimethylformamide and cooled with an ice water bath. 8.5 g (37.5 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution, after which the mixture is stirred for 15 minutes. Then, 7.87 g (25 mmoles) of (Z)-α-(5-bromo)-isatinylidene-2,6-dimethylpyridine (see Example 7) are added to the solution and stirred for 2 hours while the ice bath melts. The reaction mixture is then evaporated to dryness under vacuum. The evaporation residue is dissolved in a mixture of ethyl acetate and water (300 + 100 m*L*), and the phases are separated. The aqueous phase is extracted with ethyl acetate (2 x 100 m*L*) and the

organic phases combined are washed with 2 x 100 m*L* of water and dried over anhydrous sodium sulfate. The filtered solution is concentrated by evaporation to about 20-30 m*L*, the crystalline substance precipitated is filtered and washed with cold ethyl acetate. 4.3 g of the title compound are thus obtained..

Yield: 52.3%

Melting point: 190-191 °C

Elemental analysis based on the empirical formula $C_{16}H_{13[?]}N_2OBr$ (molecular weight: 329.19):

Calculated: C = 58.37%, H = 3.98% [?], N = 8.51%, Br = 24.57%.

Found: C = 58.47%, H = 4.05%, N = 8.77%, Br = 24.16%.

IR (KBr): 3420, 1705, 1680, 1620, 1600, 1580 cm^{-1}.

Example 7

(Z)-α-(5-Bromo)-isatinylidene-2,6-dimethylpyridine (II)

16.5 g (86 mmoles) of *p*-toluenesulfonic acid monohydrate are refluxed in 270 m*L* of toluene in a flask equipped with a water separator attachment for 1 hour. 9.15 g (27.5 mmoles) of α-[2-oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2,6-dimethylpyridine (see Example 8) are added to the cooled solution, and the mixture is refluxed for 3 hours. The crystalline substance precipitated is filtered out on the next day, dissolved in a mixture of water and methanol (150 + 20 m*L*) after drying, and 6 m*L* of a 40% sodium hydroxide solution are added dropwise to the solution while stirring intensely. The yellow, crystalline substance separated is filtered out, washed with 2 x 50 m*L* of water, and dried. 6.86 g of the title compound are thus obtained.

Yield: 79.3%

Melting point: 227-236°C.

Elemental analysis based on the empirical formula $C_{15[?]}H_{11}N_2OBr$ (molecular weight: 315.17):

Calculated: C = 57.15%, H = 3.51%, N = 8.88%, Br = 23.35%.

Found: C = 57.09%, H = 3.55%, N = 8.92%, Br = 23.30%.

IR (KBr): 3400, 1690, 1600, 1580 cm^{-1}.

Example 8

α-[2-Oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2,6-dimethylpyridine (III)

2.44 g of 5-bromoisatin monohydrate (10 mmoles) are suspended in 5 m*L* of 2,6-dimethylpyridine, and then stirred at 120-130°C for 3 hours. The reaction mixture, cooled to room temperature, solidifies. About 20 m*L* of water are added to this mixture, the solid crystalline substance is filtered and rinsed with 10-20 m*L* of ether. 2.35 g of the title compound are thus obtained.

Yield:	70.8%
Melting point:	185-187°C
IR (KBr):	3300, 1710, 1610, 1600, 1590 cm^{-1}.

Example 9

1,3-1-([5-Methyl]-2-pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-{3H}-indol]-2'(1'H)-one (1408470, 3β)

2.5 g of sodium hydride dispersion are made oil-free by washing with *n*-hexane under an argon atmosphere, then dissolved in 75 m*L* of anhydrous dimethylformamide and cooled with an ice water bath. 8.5 g (37.5 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution, and the mixture is then stirred for 15 minutes. 7.87 g (25 mmoles) of (Z)-α-(5-bromo)-isatinylidene-2,5-dimethylpyridine (see Example 10) are then added to the solution, and the mixture is then stirred for 2 hours while the ice bath melts. The reaction mixture is evaporated to dryness under vacuum. The evaporation residue is dissolved in a mixture of ethyl acetate + water (300 +

100 mL), and the phases are separated. The aqueous portion is extracted with 2 x 100 mL of ethyl acetate, the organic phases combined are washed with 2 x 100 mL of water and dried over anhydrous sodium sulfate. The filtered solution is concentrated by evaporation to about 20-30 mL under vacuum, and the crystalline substance precipitated is filtered off and washed with cold ethyl acetate. 4.79 g of the title compound are thus obtained.

Yield:	58.3%
Melting point:	221-223°C

Two g of the above product are dissolved hot in 80 mL of acetone for recrystallization, clarified with animal charcoal, and concentrated by evaporation to about 10 mL under vacuum. The crystalline substance precipitated is filtered, washed with about 5 mL of cold acetone, and dried. 1.4 g of the title compound are thus obtained.

Melting point:	226-228°C
IR (KBr):	3300, 1700, 1620 cm^{-1}.

Example 10

(Z)-α-(5-Bromo)-isatinylidene-2,5-dimethylpyridine (II)

Fifteen g (78.8 mmoles) of *p*-toluenesulfonic acid monohydrate are refluxed in 250 mL of toluene in a flask equipped with a water separator attachment for 1 hour. 8.3 g (25 mmoles) of α-[2-oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2,5-dimethylpyridine (Example 11) are added to the cooled solution, and the mixture is refluxed for 5 hours. The toluene is removed under vacuum, the evaporation residue is dissolved in a mixture of water and methanol (200 + 20 mL), and the solution is alkalized with a concentrated ammonium hydroxide solution. The yellow, crystalline substance precipitated is filtered off, washed with 3 x 50 mL of water, and dried. 7.4 g of the title compound are thus obtained.

Yield:	94.0%
Melting point:	188-197°C.
IR (KBr):	3300, 1720, 1700 cm^{-1}.

Example 11

α-[2-Oxo-3-hydroxy-5-bromo-indolinyl-(3)]-2,5-dimethylpyridine (III)

9.76 g of 5-bromoisatin monohydrate (40 mmoles) are suspended in 20 m*L* of 2,5-lutidine, and then stirred for 3.5 hours at 120-130°C. After cooling, the reaction mixture is cooled with an ice water bath, the crystalline substance precipitated is filtered off, and washed with 20-30 m*L* of cold ethanol. 6.41 g of the title compound are thus obtained. An additional 1.1 g of product are obtained from the wash liquid stored in a refrigerator on the next day.

Yield:	56.4%
Melting point:	218-220°C
IR (KBr):	3350, 1700, 1620, 1600 cm^{-1}.

Example 12

(±)-1,3-1-(4-Pyridyl)-spiro[cyclopropane-1,3'[3H]-indol]-2'(1'H)-one (3β)

Twenty mg of sodium hydride dispersion are made oil-free by washing with *n*-hexane under an argon atmosphere, then dissolved in 6 m*L* of anhydrous formamide, and cooled with an ice water bath. 0.63 of (3 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution within about 5 minutes, after which the mixture is stirred for another 15 minutes. 0.64 g (mmole) [sic - Tr.Ed.] of (E)-α-isatinylidene-4-methylpyridine (see Example 13) are added in small portions to the above solution, after which the mixture is stirred for 2 hours while the ice bath melts. Two m*L* of water are added to the reaction mixture, and then concentrated by evaporation under motor

vacuum. The evaporation residue is dissolved in a mixture of 40 m*L* of ethyl acetate and 10 m*L* of water. The phases are separated, the organic phase is washed with 2 x 10 m*L* of water, and then dried over anhydrous sodium sulfate. The filtered solution is concentrated by evaporation under vacuum, and the oily residue is crystallized from 5 m*L* of ethyl acetate. 0.2 g of the title compound is thus obtained.

Yield:	29.4%
Melting point:	198-200°C
IR (KBr):	3400, 1680, 1600, 1580, 1450 cm^{-1}.

Example 13

(E)-α-Isatinylidene-4-methylpyridine (II) (1407442)

16.6 g (87 mmoles) of *p*-toluenesulfonic acid monohydrate are refluxed for 1 hour using a water separator attachment. 8.4 g (20 mmoles) of α-[2-oxo-3-hydroxy-indolinyl-(3)]-4-methylpyridine are added to the cooled solution, the mixture is refluxed for 24 hours, and then evaporated to dryness. The evaporation residue is dissolved in a mixture of 500 m*L* of chloroform and 50 m*L* of water, and the pH is then adjusted to alkaline with 10 m*L* of concentrated ammonium hydroxide solution. The phases are separated, the organic phase is washed with 3 x 20 m*L* of water, and then dried with anhydrous sodium sulfate. The filtered solution is evaporated to dryness under vacuum. The 6.5 g of evaporation residue obtained are applied to a silica gel-packed column (eluent: 500 m*L* of chloroform ⟶ 800 m*L* of a mixture of chloroform + methanol at a ratio of 19:1 ⟶ 800 m*L* of a mixture of chloroform + methanol at a ratio of 9:1). The solvent is removed under vacuum after combining the identical fractions. 2.5 g of the title compound are thus obtained.

Yield:	32.0%
Melting point:	227-230°C
IR (KBr):	3400, 1690, 1600, 1580, 1450 cm^{-1}.

Example 14

(Z)-Isatinylidene-4-methylpyridine (II)

The procedure described in Example 13 is followed in every respect. Using the column chromatographic method described there, we obtain 0.4 g of the title compound.

Yield:	5.1%
Melting point:	167-171°C
IR (KBr):	1680, 1600, 1590, 1460, 1410, 1380 cm^{-1}.

Example 15

(±)-1,3-1-([4-methyl]-2-pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-[3H]-indol-2'(1'H)-one (1408320, 3β)

2.5 g of sodium hydride dispersion are made oil-free by washing with *n*-hexane under an argon atmosphere, then dissolved in 75 m*L* of anhydrous dimethylformamide and cooled with an ice water bath. 8.5 g (37.5 mmoles) of trimethylsulfoxonium iodide are added in small portions to the solution, after which the mixture is stirred for 15 minutes. Then, 7.7 g (25.2 mmoles) of (E/Z)-α-(5-bromo)-isatinylidene-4-methylpyridine (Example 16) are added to the solution, and the mixture is stirred for 2 hours while the ice bath melts. The reaction mixture is evaporated to dryness under vacuum. The evaporation residue is dissolved in a mixture of ethyl acetate and water (300 + 100 m*L*), and the phases are separated. The aqueous phase is extracted with 2 x 100 m*L* of ethyl acetate, the combined organic phases are washed with 2 x 100 m*L* of water, and dried over anhydrous sodium sulfate. The filtered solution is evaporated to dryness under vacuum. The evaporation residue is subjected to chromatography on a silica gel-packed column (eluent: Mixture of chloroform : methanol at a ratio of 19:1). The identical fractions are combined, and the solvent is removed under vacuum. 1.8 g of the title compound are thus obtained.

Yield: 16.1%

Melting point: 224-227°C

Elemental analysis based on the empirical formula $C_{15}H_{11[?]}ON_2Br$ (molecular weight: 315.15):

Calculated: C = 57.16%, H = 3.51%, N = 8.88%, Br = 23.35%.

Found: C = 57.09%, H = 3.55%, N = 8.73%, Br = 23.25%.

Example 16

(E/Z)-α-(5-bromo)-isatinylidene-4-methylpyridine (II)

Twenty-one g (0.11 mole) of *p*-toluenesulfonic acid monohydrate are refluxed in 350 m*L* of toluene for 1 hour in a flask equipped with a water separator attachment. 12.76 g (35 mmoles) of α-(2-oxo-3-hydroxy-(5-bromo)-indolinyl-(3)-4-methylpyridine (Example 17) are added to the cooled solution and refluxed for 4 hours. The crystalline substance is filtered out of the reaction mixture on the next day, this crystalline substance is dissolved after drying in a mixture of water + methanol (250 + 25 m*L*), and 10 m*L* of a 40% sodium hydroxide solution are added to it dropwise. The yellow crystalline substance precipitated is filtered off, washed with 2 x 50 m*L* of water, rinsed with ether, and dried. 9.0 g of the title compound (E:Z = 65%:35%, based on NMR measurement) are thus obtained.

Yield: 74.8%.

Example 17

α-[2-Oxo-3-hydroxy-(5-bromo)-indolinyl-(3)]-4-methylpyridine (III)

12.2 g of 5-bromoisatin monohydrate (50 mmoles) are suspended in 15 m*L* of 4-picoline, and then boiled under a reflux cooler (145°C). A clear solution is obtained at this temperature, and the reaction mixture then solidifies into a crystal mass after about 5-10 minutes. The reaction mixture is allowed to cool and 20 m*L* of ethanol are then added to it. The mixture is then refluxed for another 0.5 hour. The crystalline substance is filtered out of the reaction mixture cooled to room

temperature, washed with 20 m*L* of ethanol, and dried. 14.46 g of the title compound are thus obtained.

Yield:	90.6%
Melting point:	234-236°C
IR (KBr):	3400, 1700, 1605, 1595 cm^{-1}.

Patent Claims

1. Process for preparing racemic and optically active 3-spiro-oxindole derivatives according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom, and

Z and W denote, independently from one another, a nitrogen atom or a =CH- or =CR- group, in which R denotes an alkyl group containing 1-4 carbon atoms, providing that Z and W cannot denote a nitrogen atom at the same time,

and therapeutically suitable acid addition salts thereof,

characterized in that an isatinylidene derivative according to the general formula (II), in which X, W, Z, and R have the same meanings as above, is reacted with trimethylsulfoxonium methylide prepared in situ in an organic solvent, under an inert gas atmosphere, and, after separating the C_3 isomers, the compounds according to the general formula (I) obtained are optionally resolved and/or converted into the therapeutically suitable acid addition salts.

2. Process in accordance with claim 1, **characterized in that** the reaction is carried out under an argon atmosphere in an organic dipolar aprotic solvent at a temperature of 0-25°C.

3. Process for preparing a drug preparation, **characterized in that** a compound according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom, and

Z and W denote, independently from one another, a nitrogen atom or =CH- or =CR-, in which R denotes an alkyl group containing 1-4 carbon atoms,

providing that Z and W cannot denote a nitrogen atom at the same time, or a therapeutically suitable acid addition salt thereof is converted into a drug preparation by mixing with vehicle substances and/or inactive ingredients usually used in the pharmaceutical industry.

4 Racemic and optically active 3-spiro-oxindole derivatives according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom, and

Z and W denote, independently from one another, a nitrogen atom or a =CH- or =CR- group,

in which R denotes an alkyl group containing 1-4 carbon atoms,

providing that Z and W cannot denote a nitrogen atom at the same time, and therapeutically suitable acid addition salts thereof.

5. (±)-1,3-1-(2-pyridyl)-spiro[cyclopropane-1,3'-(5-bromo)-[3H]-indol]-2'(1'H)-one and therapeutically suitable acid addition salts thereof.

6. Drug preparation, **characterized in that** it contains a compound according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom, and

Z and W denote, independently from one another, a nitrogen atom or a =CH- or =CR- group, in which R denotes an alkyl group containing 1-4 carbon atoms,

providing that Z and W cannot denote a nitrogen atom at the same time, or therapeutically suitable acid addition salts thereof, along with vehicle substances and/or inactive ingredients usually used in the drug industry.

Erik Bogsch

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Process for Preparing Spiro-oxindole Derivatives and of Drug Preparations Containing Same

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Application date: Dec. 10, 1992

ABSTRACT

The present invention pertains to a process for preparing the novel racemic and optically active 3-spiro-oxindole derivatives according to the general formula (I), in which

X denotes a hydrogen atom or a halogen atom, and

Z and W denote, independently from one another, a nitrogen atom or a =CH- or =CR- group, in which R denotes an alkyl group containing 1-4 carbon atoms,

providing that Z and W cannot denote a nitrogen atom at the same time, and therapeutically suitable acid addition salts thereof by reacting an isatinylidene derivative according to the general formula (II), in which X, W, Z and R have the meanings given above, with trimethylsulfoxonium methylide prepared in situ, in an inert solvent under an inert atmosphere and by optionally resolving the compounds according to the general formula (I) obtained after the separation of the C_3 isomers and/or converting them into therapeutically suitable acid addition salts. The compounds according to the present invention possess antihypoxic and anticonvulsive actions and inhibitory action against established edema.

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Richter Gedeon Vegyészeti Gyár Rt.

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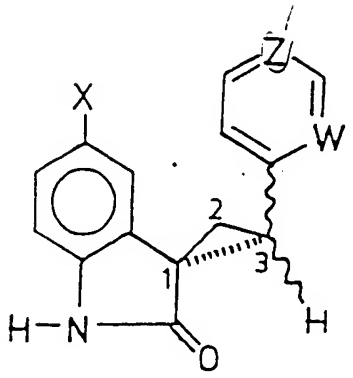

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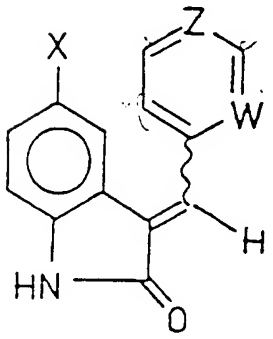

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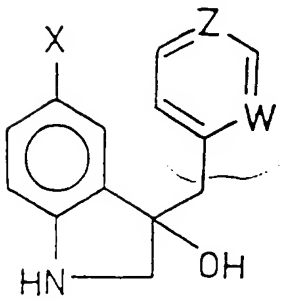

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